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09/897,801	06/29/2001	Thomas C. Pinkerton	6794S-000019US	1264

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EXAMINER

AZPURU, CARLOS A

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>09/897,801</b>	Applicant(s) <b>Pinkerton</b>
	Examiner <b>Carlos Azpuru</b>	Art Unit <b>1615</b>

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)  Responsive to communication(s) filed on Sep 26, 2002

2a)  This action is **FINAL**.      2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4)  Claim(s) 85-138 is/are pending in the application.

4a) Of the above, claim(s) 117 and 118 is/are withdrawn from consideration.

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 85-116 and 119-138 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are a)  accepted or b)  objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)  The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)  All b)  Some\* c)  None of:

1.  Certified copies of the priority documents have been received.

2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)  The translation of the foreign language provisional application has been received.

15)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)  Notice of References Cited (PTO-892)

4)  Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_

2)  Notice of Draftsperson's Patent Drawing Review (PTO-948)

5)  Notice of Informal Patent Application (PTO-152)

3)  Information Disclosure Statement(s) (PTO-1449) Paper No(s). 12

6)  Other:

## DETAILED ACTION

Receipt is acknowledged of the information disclosure statement, election, and amendment filed 09/26/02.

### ***Election/Restrictions***

Applicant's election without traverse of Group I, claims 85-116 and 119-138 in Paper No. 14 is acknowledged.

Claims 117-118 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or  
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or  
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 85-116, 119-138 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Pettis et al (reference designation #7 on IDS).

Pettis et al disclose a method for delivering intradermally, with improvement over subcutaneous injection (see Abstract, claims 25 and 47). The bioactives delivered may be any of those described in paragraph [0051], page 7, and specifically include dopamine agonists, growth hormone, as well as low, molecular weight heparin. Nanoparticles are described at paragraph [0048], page 7. Needles and microneedles are found at page 4, paragraph [0027]. Electroporation and thermal poration are found at page 4, paragraph [0025]. Bolus injection is described at page 3, paragraph [0022]. The instant claims are clearly anticipated by Pettis et al.

? pg 6

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlos A. Azpuru whose telephone number is 703/308-0237. The examiner can normally be reached on Tu-Fri, 6:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

ca  
October 9, 2002



CARLOS AZPURU  
PRIMARY EXAMINER  
GROUP 1500

**INTRADERMAL DELIVERY OF SUBSTANCES****INVENTORS:**

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**FIELD OF THE INVENTION**

The present invention relates to methods and devices for administration of substances into the skin.

10

**BACKGROUND OF THE INVENTION**

Conventional needles have long been used to deliver drugs and other substances to humans and animals through the skin, and considerable effort has been made to achieve reproducible and efficacious delivery through the skin while reducing or eliminating the pain associated with conventional needles. Certain transdermal delivery systems eliminate needles entirely, and rely on chemical mediators or external driving forces such as iontophoretic currents or sonophoresis to breach the stratum corneum painlessly and deliver substances through the skin. However, such transdermal delivery systems are not sufficiently reproducible and give variable clinical results.

Mechanical breach of the stratum corneum is still believed to be the most reproducible method of administration of substances through the skin, and it provides the greatest degree of control and reliability. Intramuscular (IM) and subcutaneous (SC) injections are the most commonly used routes of administration. The dermis lies beneath the stratum corneum and epidermis, beginning at a depth of about 60-120  $\mu$ m below the skin surface in humans, and is approximately 1-2 mm thick. However, intradermal (ID) injection is rarely used due to the difficulty of correct needle placement in the intradermal space, the difficulty of maintaining placement of the needle in the intradermal space, and a lack of information and knowledge of the pharmacokinetic profiles for many drugs delivered ID. In addition, little is known about fluid absorption limits in dermal tissue and the effect of depot time on drug stability. However, ID administration of drugs and other substances may have several advantages. The intradermal space is close to the capillary bed to allow for absorption and systemic distribution of the substance but is above the peripheral nerve net which may reduce or eliminate injection pain. In addition, there are more suitable and accessible ID injection sites available for a patient as compared to currently recommended SC administration sites (essentially limited to the abdomen and thigh).

Recent advances in needle design have reduced the pain associated with injections. Smaller gauge and sharper needles reduce tissue damage and therefore decrease the amount of inflammatory mediators released. Of particular interest in this regard are microneedles, which are typically less than 0.2 mm in width and less than 2 mm in length. They are usually fabricated from silicon, plastic or metal  
5 and may be hollow for delivery or sampling of substances through a lumen (see, for example, US Patent No. 3,964,482; US Patent No. 5,250,023; US Patent No. 5,876,582; US Patent No. 5,591,139; US Patent No. 5,801,057; US Patent No. 5,928,207; WO 96/17648) or the needles may be solid (see, for example, US Patent No. 5,879,326; WO 96/37256). By selecting an appropriate needle length, the depth of penetration of the microneedle can be controlled to avoid the peripheral nerve net of the skin and  
10 reduce or eliminate the sensation of pain. The extremely small diameter of the microneedle and its sharpness also contribute to reduced sensation during the injection. Microneedles are known to mechanically porate the stratum corneum and enhance skin permeability (US Patent No. 5,003,987). However, the present inventors have found that, in the case of microneedles, breaching the stratum corneum alone is not sufficient for clinically efficacious intradermal delivery of substances. That is,  
15 other factors affect the ability to deliver substances intradermally via small gauge needles in a manner which produces a clinically useful response to the substance.

US Patent No. 5,848,991 describes devices for the controlled delivery of drugs to a limited depth in the skin corresponding to about 0.3-3.0 mm and suggests that such devices are useful for delivery of a variety of drugs, including hormones. US Patent No. 5,957,895 also describes a device for the controlled delivery of drugs wherein the needle may penetrate the skin to a depth of 3 mm or less. The fluid in the pressurized reservoir of the device is gradually discharged under gas pressure through the needle over a predetermined interval, e.g., a solution of insulin delivered over 24 hrs. Neither of these patents indicates that delivery using the devices produces a clinically useful response. Kaushik, et al. have described delivery of insulin into the skin of diabetic rats via microneedles with a detectable reduction in blood glucose levels. These authors do not disclose the depth of penetration of the microneedles nor do they report any results suggesting a clinically useful glucose response using this method of administration. Further, there is no evidence of accurate or reproducible volume of delivery using such a device. WO 99/64580 suggests that substances may be delivered into skin via microneedles at clinically relevant rates. However, it fails to appreciate that clinical efficacy is  
20 dependent upon both accurate, quantitative, and reproducible delivery of a volume or mass of drug substance and the pharmacokinetic uptake and distribution of that substance from the dermal tissue.  
25

#### SUMMARY OF THE INVENTION

35 The present invention improves the clinical utility of ID delivery of drugs and other substances to humans or animals. The methods employ small gauge needles, especially microneedles, placed in

the intradermal space to deliver the substance to the intradermal space as a bolus or by infusion. It has been discovered that the placement of the needle outlet within the skin is critical for efficacious delivery of active substances via small gauge needles to prevent leakage of the substance out of the skin and to improve absorption within the intradermal space. ID infusion is a preferred method for 5 delivery according to the invention because lower delivery pressures are required. This also reduces the amount of substance lost to the skin surface due to internal pressure which increases as fluid accumulates within the skin prior to absorption. That is, infusion minimizes effusion of the substance out of the tissue. Infusion also tends to reduce painful swelling and tissue distension and to reduce internal pressure as compared to the corresponding bolus dose. The pharmacokinetics of hormone 10 drugs delivered according to the methods of the invention have been found to be very similar to the pharmacokinetics of conventional SC delivery of the drug, indicating that ID administration according to the methods of the invention is likely to produce a similar clinical result (i.e., similar efficacy) with the advantage of reduction or elimination of pain for the patient. Delivery devices which place the needle outlet at an appropriate depth in the intradermal space and control the volume and rate of fluid delivery 15 provide accurate delivery of the substance to the desired location without leakage.

#### DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates the results of Example 1 for plasma insulin levels during SC and ID infusion of 20 insulin.

Fig. 2 illustrates the results of Example 1 for blood glucose levels during SC and ID infusion of insulin.

Fig. 3 illustrates the results of Example 1 for plasma PTH levels during SC and ID infusion of PTH.

Fig. 4 illustrates the results of Example 2 for plasma insulin levels during SC and ID infusion of insulin at 2 U/hr.

Fig. 5 illustrates the results of Example 2 for plasma glucose levels during SC and ID infusion of insulin at 2 U/hr.

The present invention provides delivery of a drug or other substance to a human or animal subject via a device which penetrates the skin to the depth of the intradermal space. The drug or substance is administered into the intradermal space through one or more hollow needles of the device. 35 Substances infused according to the methods of the invention have been found to exhibit pharmacokinetics similar to that observed for the same substance administered by SC injection, but the

ID injection is essentially painless. The methods are particularly applicable to hormone therapy, including insulin and parathyroid hormone (PTH) administration.

The injection device used for ID administration according to the invention is not critical as long as it penetrates the skin of a subject to a depth sufficient to penetrate the intradermal space without

5 passing through it. In most cases, the device will penetrate the skin to a depth of about 0.5-3 mm, preferably about 1-2 mm. The devices may comprise conventional injection needles, catheters or microneedles of all known types, employed singly or in multiple needle arrays. The terms "needle" and "needles" as used herein are intended to encompass all such needle-like structures. The needles are preferably of small gauge such as microneedles (i.e., smaller than about 25 gauge; typically about 27-

10 35 gauge). The depth of needle penetration may be controlled manually by the practitioner, with or without the assistance of indicator means to indicate when the desired depth is reached. Preferably, however, the device has structural means for limiting skin penetration to the depth of the intradermal space. Such structural means may include limiting the length of the needle or catheter available for penetration so that it is no longer than the depth of the intradermal space. This is most typically

15 accomplished by means of a widened area or "hub" associated with the shaft of the needle, or for needle arrays may take the form of a backing structure or platform to which the needles are attached (see, for example, US Patent 5,879,326; WO 96/37155; WO 96/37256). Microneedles are particularly well suited for this purpose, as the length of the microneedle is easily varied during the fabrication

20 process and microneedles are routinely produced in less than 1 mm lengths. Microneedles are also very sharp and of very small gauge (typically about 33 gauge or less) to further reduce pain and other sensation during the injection or infusion. They may be used in the invention as individual single-lumen microneedles or multiple microneedles may be assembled or fabricated in linear arrays or two-dimensional arrays to increase the rate of delivery or the amount of substance delivered in a given period of time. Microneedles may be incorporated into a variety of devices such as holders and housings

25 which may also serve to limit the depth of penetration or into catheter sets. The devices of the invention may also incorporate reservoirs to contain the substance prior to delivery or pumps or other means for delivering the drug or other substance under pressure. Alternatively, the device housing the microneedles may be linked externally to such additional components.

It has been found that certain features of the intradermal administration protocol are essential 30 for clinically useful pharmacokinetics and dose accuracy. First, it has been found that placement of the needle outlet within the skin significantly affects these parameters. The outlet of a smaller gauge needles with a bevel has a relatively large exposed height (the vertical "rise" of the outlet). Although the needle tip may be placed at the desired depth within the intradermal space, the large exposed height of the needle outlet allows the substance being delivered to be deposited at a much shallower

35 depth nearer the skin surface. As a result, the substance tends to effuse out of the skin due to backpressure exerted by the skin itself and to pressure built up from accumulating fluid from the

injection or infusion. For example, 200  $\mu\text{m}$  microneedles are often cited as suitable means for delivery of substances through the skin. We have found, however, that even if the needle outlet is at the tip of such a microneedle (without any bevel) the substance is deposited at too shallow a depth to allow the skin to seal around the needle and the substance readily effuses onto the surface of the skin. Shorter 5 microneedles such as these serve only to permeabilize the skin and do not give sufficient dose control for clinical utility. In contrast, microneedles according to the invention have a length sufficient to penetrate the intradermal space (the "penetration depth") and an outlet at a depth within the intradermal space (the "outlet depth") which allows the skin to seal around the needle against the backpressure which tends to force the delivered substance toward the skin surface. In general, the 10 needle is no more than about 2 mm long, preferably about 300  $\mu\text{m}$  to 2 mm long, most preferably about 500  $\mu\text{m}$  to 1 mm long. The needle outlet is typically at a depth of about 250  $\mu\text{m}$  to 2 mm when the needle is inserted in the skin, preferably at a depth of about 750  $\mu\text{m}$  to 1.5 mm, and most preferably at a depth of about 1 mm. The exposed height of the needle outlet and the depth of the outlet within the intradermal space influence the extent of sealing by the skin around the needle. That 15 is, at a greater depth a needle outlet with a greater exposed height will still seal efficiently whereas an outlet with the same exposed height will not seal efficiently when placed at a shallower depth within the intradermal space. Typically, the exposed height of the needle outlet will be from 0 to about 1 mm, preferably from 0 to about 300  $\mu\text{m}$ . A needle outlet with an exposed height of 0 has no bevel and is at the tip of the needle. In this case, the depth of the outlet is the same as the depth of penetration of 20 the needle. A needle outlet which is either formed by a bevel or by an opening through the side of the needle has a measurable exposed height.

Second, it has been found that the pressure of injection or infusion must be carefully controlled due to the high backpressure exerted during ID administration. Gas-pressure driven devices as are known in the prior art are prone to deviations in delivery rate. It is therefore preferable to deliver the 25 substance by placing a constant pressure directly on the liquid interface, as this provides a more constant delivery rate which is essential to optimize absorption and to obtain the desired pharmacokinetics. Delivery rate and volume are also desirably controlled to prevent the formation of weals at the site of delivery and to prevent backpressure from pushing the needle out of the skin. The appropriate delivery rates and volumes to obtain these effects for a selected substance may be 30 determined experimentally using only ordinary skill. That is, in general the size of the weal increases with increasing rate of delivery for infusion and increases with increasing volume for bolus injection. However, the size and number of microneedles and how closely together they are placed can be adjusted to maintain a desired delivery rate or delivery volume without adverse effects on the skin or the stability of the needle in the skin. For example, increasing the spacing between the needles of a 35 microneedle array device or using smaller diameter needles reduces the pressure build-up from unabsorbed fluid in the skin. Such pressure causes weals and pushes the needle out of the skin. Small

diameter and increased spacing between multiple needles also allows more rapid absorption at increased rates of delivery or for larger volumes. In addition, we have found that ID infusion or injection often provides higher plasma levels of drug than conventional SC administration, particularly for drugs which are susceptible to *in vivo* degradation or clearance. This may, in some cases, allow for smaller doses of the substance to be administered through microneedles via the ID route, further reducing concerns about blistering and backpressure.

The administration methods contemplated by the invention include both bolus and infusion delivery of drugs and other substances to human or animal subjects. A bolus dose is a single dose delivered in a single volume unit over a relatively brief time period, typically less than about 5-10 min.

10 Infusion administration comprises administering a fluid at a selected rate (which may be constant or variable) over a relatively more extended time period, typically greater than about 5-10 min. To deliver a substance according to the invention, the needle is placed in the intradermal space and the substance is delivered through the lumen of the needle into the intradermal space where it can act locally or be absorbed by the bloodstream and distributed systemically. The needle may be connected to a reservoir  
15 containing the substance to be delivered. Delivery from the reservoir into the intradermal space may occur either passively (without application of external pressure to the substance to be delivered) or actively (with the application of pressure). Examples of preferred pressure-generating means include pumps, syringes, elastomeric membranes, osmotic pressure or Belleville springs or washers. See, for example, US Patent No. 5,957,895; US Patent No. 5,250,023; WO 96/17648; WO 98/11937; WO  
20 99/03521. If desired, the rate of delivery of the substance may be variably controlled by the pressure-generating means. As a result, the substance enters the intradermal space and is absorbed in an amount and at a rate sufficient to produce a clinically efficacious result. By "clinically efficacious result" is meant a clinically useful biological response resulting from administration of a substance. For example, prevention or treatment of a disease or condition is a clinically efficacious result, such as  
25 clinically adequate control of blood sugar levels (insulin), clinically adequate management of hormone deficiency (PTH, Growth Hormone), expression of protective immunity (vaccines), or clinically adequate treatment of toxicity (antitoxins). As a further example, a clinically efficacious result also includes control of pain (e.g., using triptans, opioids, analgesics, anesthetics, etc.), thrombosis (e.g., using heparin, coumadin, warfarin, etc.) and control or elimination of infection (e.g., using antibiotics).

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### EXAMPLE 1

ID infusion of insulin was demonstrated using a stainless steel 30 gauge needle bent at the tip at a 90° angle such that the available length for skin penetration was 1-2 mm. The needle outlet (the tip of the needle) was at a depth of 1.7-2.0 mm in the skin when the needle was inserted and the total exposed height of the needle outlet was 1.0-1.2 mm. The needle was constructed in a delivery device

similar to that described in US Patent No. 5,957,895, with infusion pressure on the insulin reservoir provided by a plastic Belleville spring and gravimetrically measured flow rates of 9 U/hr (90  $\mu$ L/hr). The corresponding flow rates for SC control infusions were set using MiniMed 507 insulin infusion pumps and Disetronic SC catheter sets. Basal insulin secretion in swine was suppressed by infusion of 5 octreotide acetate (Sandostatin®, Sandoz Pharmaceuticals, East Hanover, NJ), and hyperglycemia was induced by concomitant infusion of 10% glucose. After a two hour induction and baseline period insulin was infused for 2 hr., followed by a 3 hr. washout period. Plasma insulin levels were quantitated via a commercial radio-immunoassay (Coat-A-Count® insulin, Diagnostic Products Corporation, Los Angeles, CA), and blood glucose values were measured with a commercial monitor (Accu-chek 10 Advantage®, Boehringer Mannheim Corp, Indianapolis, IN). Weight normalized plasma insulin levels and corresponding blood glucose values are shown in Fig. 1 and Fig. 2. Data indicate similar plasma insulin levels and onset periods for infusion via the ID route and via the conventional SC route. The decrease in blood glucose response is also similar between the two. Although 9 U/hr. is a higher administration rate than is typically used medically, these results also demonstrate the ability of dermal 15 tissues to readily absorb and distribute medicaments which are infused via this pathway.

20 A similar experiment was conducted using human parathyroid hormone 1-34 (PTH). PTH was infused for a 4 hr. period, followed by a 2 hr. clearance. Flow rates were controlled by a Harvard syringe pump. Control SC infusion was through a standard 31 gauge needle inserted into the SC space lateral to the skin using a "pinch-up" technique. ID infusion was through the bent 30 gauge needle described above. A 0.64 mg/mL PTH solution was infused at a rate of 75  $\mu$ L/hr. Weight normalized PTH plasma levels are shown in Fig. 3. This data demonstrates the efficacy of this route of administration for additional hormone drugs, and indicates that ID infusion may actually provide higher plasma levels for drugs that are susceptible to *in vivo* biological degradation or clearance.

25

EXAMPLE 2

ID insulin delivery was demonstrated in swine using a hollow silicon microneedle connected to a standard catheter. The catheter was attached to a MiniMed 507 insulin pump for control of fluid delivery.

30 A hollow, single-lumen microneedle (2 mm total length and 200 X 100  $\mu$ m OD, corresponding to about 33 gauge) with an outlet 1.0  $\mu$ m from the tip (100  $\mu$ m exposed height) was fabricated using processes known in the art (US Patent No. 5,928,207) and mated to a microbore catheter commonly used for insulin infusion (Disetronic). The distal end of the microneedle was placed into the plastic catheter and cemented in place with epoxy resin to form a depth-limiting hub. The needle outlet was 35 positioned approximately 1 mm beyond the epoxy hub, thus limiting penetration of the needle outlet into the skin to approximately 1 mm., which corresponds to the depth of the intradermal space in

swine. The patency of the fluid flow path was confirmed by visual observation, and no obstructions were observed at pressures generated by a standard 1 cc syringe. The catheter was connected to an external insulin infusion pump (MiniMed 507) via the integral Luer connection at the catheter outlet.

The pump was filled with Humalog™ (LisPro) insulin (Lilly) and the catheter and microneedle were primed with insulin according to the manufacturer's instructions. Sandostatin® solution was administered via IV infusion to an anesthetized swine to suppress basal pancreatic function and insulin secretion. After a suitable induction period and baseline sampling, the primed microneedle was inserted perpendicular to the skin surface in the flank of the animal up to the hub stop. Insulin infusion was begun at a rate of 2 U/hr and continued for 4.5 hr. Blood samples were periodically withdrawn and analyzed for serum insulin concentration and blood glucose values using the procedures of Example 1. Baseline insulin levels before infusion were at the background detection level of the assay, as shown in Fig. 4. After initiation of the infusion, serum insulin levels showed an increase which was commensurate with the programmed infusion rates. Blood glucose levels also showed a corresponding drop relative to negative controls (NC) and this drop was similar to the drop observed for conventional SC infusion (Fig. 5).

In this experiment, the microneedle was demonstrated to adequately breach the skin barrier and deliver a drug *in vivo* at pharmaceutically relevant rates. The ID infusion of insulin was demonstrated to be a pharmacokinetically acceptable administration route, and the pharmacodynamic response of blood glucose reduction was also demonstrated. This data indicates a strong probability of successful pharmacological results for ID administration of hormones and other drugs in humans according to the methods of the invention.

**WHAT IS CLAIMED IS:**

1. A method for delivering a substance into skin comprising delivering the substance into an intradermal space within the skin through a small gauge needle inserted into the intradermal space, wherein an outlet of the needle is inserted at a depth within the skin such that leakage of the substance to the surface of the skin is substantially prevented.

2. The method of Claim 1 wherein the needle is selected from the group consisting of microneedles, catheter needles, and injection needles.

3. The method of Claim 1 wherein a single needle is inserted.

4. The method of Claim 1 wherein multiple needles are inserted.

5. The method of Claim 1 wherein the substance is a liquid delivered by pressure directly on the liquid.

6. The method of Claim 1 wherein a hormone is delivered.

7. The method of Claim 6 wherein the hormone is selected from the group consisting of insulin and PTH.

8. The method of Claim 1 wherein the substance is infused.

9. The method of Claim 1 wherein the substance is injected as a bolus.

10. The method of Claim 1 wherein the needle is about 300  $\mu$ m to 2 mm long.

11. The method of Claim 10 wherein the needle is about 500  $\mu$ m to 1 mm long.

12. The method of Claim 1 wherein the outlet is at a depth of about 250  $\mu$ m to 2 mm when the needle is inserted.

13. The method of Claim 12 wherein the outlet is at a depth of about 750  $\mu$ m to 1.5 mm when the needle is inserted.

14. The method of Claim 12 wherein the outlet has an exposed height of about 0 to 1 mm.
15. The method of Claim 14 wherein the outlet has an exposed height of about 0 to 300  $\mu\text{m}$
- 5 16. The method of Claim 1 wherein delivery rate or volume delivered is controlled by spacing of multiple needles, needle diameter or number of needles.
- 10 17. A needle for intradermal delivery of a substance into skin comprising means for limiting penetration of the needle into the skin and an outlet positioned such that when the needle is inserted into the skin to a depth determined by the penetration limiting means, leakage of the substance to the surface of the skin is substantially prevented.
18. The needle of Claim 17 wherein the outlet is at a depth of about 500  $\mu\text{m}$  to 2 mm when the needle is inserted into the skin.
- 15 19. The method of Claim 18 wherein the outlet is at a depth of about 750  $\mu\text{m}$  to 1.5 mm when the needle is inserted into the skin.
- 20 20. The needle of Claim 17 which is about 300  $\mu\text{m}$  to 2 mm long.
21. The needle of Claim 20 which is about 500  $\mu\text{m}$  to 1 mm long.
22. The needle of Claim 17 which is contained in a device comprising a reservoir in fluid communication with the needle.
- 25 23. The needle of Claim 22 which is contained in a device further comprising pressure-generating means for delivering the substance through the needle.
24. The needle of Claim 23 wherein the pressure-generating means provides variable control of substance delivery rate.
- 30

*Add A7*

ABSTRACT

The present invention provides improved methods for ID delivery of drugs and other substances to humans or animals. The methods employ small gauge needles, especially microneedles, 5 placed in the intradermal space to deliver the substance to the intradermal space as a bolus or by infusion. It has been discovered that the placement of the needle outlet within the skin and the exposed height of the needle outlet are critical for efficacious delivery of active substances via small gauge needles to prevent leakage of the substance out of the skin and to improve absorption within the intradermal space. The pharmacokinetics of hormone drugs delivered according to the methods of the 10 invention have been found to be very similar to the pharmacokinetics of conventional SC delivery, indicating that ID administration according to the methods of the invention is likely to produce a similar clinical result (i.e., similar efficacy) with the advantage of reduction or elimination of pain for the patient. Delivery devices which place the needle outlet at an appropriate depth in the intradermal 15 space and control the volume and rate of fluid delivery provide accurate delivery of the substance to the desired location without leakage.

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